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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/758,033	11/27/96	CLAYMAN G	INGN:022

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EXAMINER	
HAUDA,K	
ART UNIT	**PAPER NUMBER**
1632	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/758,033	Applicant(s) Clayman, G.
	Examiner Karen M. Hauda	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Aug 20, 1998* .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-14, 16-20, 26-77, and 80-145* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-14, 16-20, 26-77, and 80-145* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *14*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's amendment was filed August 20, 1998. Claims 1-14, 16-20, 26-77, and 80-145 are pending and under examination.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Claim Rejections - 35 USC § 112

The prior rejection of claims 1-14, 16-20, 26-32, 36-68, 73-77, and 80-103, 108-132 and 137 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the scope of the claimed invention, is withdrawn in view of applicant's amendment to the claims filed August 20, 1998, paper # 13.

Claims 33-35, 69-72, 104-107, 133-136, 140, 141, 144 and 145, as originally filed, newly amended or newly added, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 33-35, 69-72, 104-107 and 133-136 are drawn to combination therapy. Applicants argue that the combination claims do not require that the second gene have a therapeutic response and, therefore, the rejection lacks legal basis. Applicants argue that "[i]f the p53 administration alone is sufficient to enable a claim for inhibiting tumor growth, then dependent claims which merely add other genes must also be enabled, whether or not the other genes have an effect." Applicant's arguments have been carefully considered, but are not deemed persuasive.

It is initially noted that claims 34, 35, 71, 72, 106, 107, 135 and 136, specifically require a "second **therapeutic** gene" (emphasis added). Thus, these claims clearly imply and incorporate a therapeutic benefit. Furthermore, when any of the claims are read in light of the specification, it is clear that a therapeutic benefit for the second protein or gene is intended (see page 41 of the specification). However, applicants specification fails to enable the delivery of proteins or cytokines for the numerously combined therapies claimed. Each of these different cytokines or cancer related genes has drastically different mechanistic action for which the effects upon the immune system are unpredictable. It would have required undue experimentation for one of skill in the art to determine which combinations of the numerously claimed combinations would result in a therapeutic effect which is not deleterious to the therapeutic effects of p53 given the unpredictability of the art, the breadth of the claims, the state of the art, the absence of teachings in the specification, and the absence of working examples for combination therapy. Thus, for the reasons set forth in the office action mailed February 17, 1998, paper # 10, pages 3-5, the rejection is maintained.

With respect to newly added claims 140, 141, 144 and 145 it is unclear how an intravenous or oral delivery of a nucleic acid construct can encompass delivery directly to a solid tumor. These delivery modalities are systemic and, thus, do not constitute directly delivery. The specification fails to describe how these delivery methodologies are carried out to encompass direct delivery of a viral expression construct to a solid tumor such that one of skill in the art could practice the claimed invention without undue experimentation.

The prior rejection of claims 1, 38, 74, and 109, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendment.

Claims 1-14, 16-20, 26-37, 74-77 and 80-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 140 and 144 are directed to intravenous delivery of a viral expression construct directly to a solid tumor. However, it is unclear how intravenous delivery can be considered direct administration to a solid tumor, rendering the metes and bounds of "directly administering to said tumor" in the independent claims indefinite. [Note all other claims depend from independent claims 1 and 74.]

Claim Rejections - 35 USC § 102

The prior rejection of claims 1, 3, 11, 15, 16, and 26 under 35 U.S.C. 102(a) as being anticipated by Liu et al. (Cancer Research, Vol. 55 (1995)) or Clayman et al. (Cancer Research, Vol. 55 (1995)), is withdrawn in view of applicants submission of a Declaration under 37 C.F.R. § 1.131 by Dr. Clayman.

Claim Rejections - 35 USC § 103

The prior rejection of claims 1-20, 26-37, 41, 74-108 and 114 under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Cancer Research, Vol. 55 (1995)) or Clayman et al. (Cancer Research, Vol. 55 (1995)) taken with Zhang et al. or Brahmwell is withdrawn in view of applicants submission of a Declaration under 37 C.F.R. § 1.131 by Dr. Clayman.

Claims 38-68, 73, 109-132 and 137 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) in view of Zhang et al. or Brahmwell.

Applicants argue that none of the cited references teach treatment of microscopic residual cancer (claim 38) or continuous perfusion (claim 109) and that these treatment methodologies are not obvious variations of the claimed invention. Applicant's arguments have been carefully considered, but are not deemed persuasive.

Each of Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) taught *in vivo* delivery and expression of p53 protein into tumors using

adenoviral vectors which resulted in inhibition of tumor growth. Applicants argue that continuous perfusion is not taught by the references, however, continuous perfusion is a relative term such that a single injection into a tumor is continuous perfusion during the time the injection is being performed. Thus, both Liu et al. and Wills et al. taught continuous perfusion. Furthermore, it was well known in the art at the time of the claimed invention that the longer the vector is in contact with the cell, the greater the transduction efficiency. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perfuse the tumor site with adenovirus for periods longer than a single injection for the added benefit of achieving greater transduction efficiency.

With respect to treating microscopic residual cancer, Zhang et al. taught the benefit of using surgery in combination with gene therapy to enhance treatment effects. At the time of the claimed invention, primary tumors were often removed from patients leaving only microscopic residual cancer. It is noted, that the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, one of ordinary skill in the art would have been motivated to treat microscopic tumors with the p53 gene as taught by Liu et al. or Wills et al. given that Zhang et al. teaches combining gene therapy with surgery.

Therefore, for the reasons presented above and in the previous office action, the rejection is maintained.

Claims 1-14, 16-20, 26-32, 36-68, 73-77, 80-132 and 137-145 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cajot et al. (PTO-1449, C57), Katayose et al. (PTO-1449, C58) or Srivastava et al. (PTO-1449, C59) taken with Wills et al. (Human Gene Therapy, Vol. 5 (1994)) or Liu et al. (Cancer Research, Vol. 54 (1994)) in view of Zhang et al. or Brahmwell.

Cajot et al. taught transfection of tumor cells which express endogenous p53 with exogenous p53 and demonstrated that these cells (Hut292DM cells) were inhibited in proliferation following transduction and expression of exogenous p53 (see entire article, especially abstract and page 6956). Cajot et al. did not teach *in vivo* treatment of tumor cells or transduction with a viral expression construct.

Katayose et al. taught transduction of MCF-7 cells which express endogenous p53 with an adenovirus vector encoding exogenous p53 protein. Expression of the exogenous p53 protein by these cells resulted in growth inhibition (see page 892, Figure 3, and page 896). Katayose et al. did not teach *in vivo* treatment of tumor cells.

Srivastava et al. taught inhibition of LNCaP cells (which express endogenous wild-type p53) following transduction with an adenoviral vector encoding wild-type p53 protein (see page 845). Additionally, at page 847, Srivastava et al. teaches *in vivo* treatment of LNCaP with exogenous p53 such that inhibition was achieved. Srivastava et al. does not teach combination therapy.

Liu et al. (Cancer Research, Vol. 54 (1994)) taught the growth suppression of squamous cell carcinoma of human head and neck cancer (SCCHN) established *in vivo* in nude mice following the administration of adenoviral vectors encoding wild-type p53. At page 3666, column 2, Liu et al. state that the regression in cancer burden in nude mice was at least 60 times more than in the experimental controls. Liu et al. did not teach that expression of wild-type p53 by SCCHN cancer cells made the cancer cells susceptible to radiation therapy.

Wills et al. (Human Gene Therapy, Vol. 5 (1994)) taught inhibition of tumor proliferation and tumorigenicity following a single injection of recombinant adenoviral vectors encoding wild-type p53 protein into carcinoma cell lines grown either *in vitro* or into established tumor *in vivo* in a nude mouse. Wills et al. additionally taught that repetitive administration of adenoviral vectors encoding wild-type p53 protein into tumor bearing animals increased the animal survival time and led to reduced tumor growth. These results were obtained in a variety of tumors at various multiplicity of infection (see Figure 4, for example). Additionally, at page 1086, column 2, Wills et al suggests that the ability to express wild-type p53 in cancer cells may increase the tumor cells susceptibility to radiation therapy or chemotherapy. Specifically, Wills et al. state:

> Due to the high prevalence of p53 mutations in human tumors, it is possible that tumors which have become refractory to chemotherapy and irradiation treatments may have become so due in part to the lack of wild-type p53. By resupplying functional p53 to these tumors, it is possible that they will now become susceptible to apoptosis normally associated with the DNA damage induced by radiation and chemotherapy.

Each of Zhang et al. or Brahmwell taught the advantage to combination therapy. Specifically, Zhang et al. reviews various treatments for cancer and concludes at page 505 that with respect to cancer therapy, combinational approaches with using gene therapy, chemotherapy, immunotherapy, radiotherapy, and surgery is the most logical and has the greatest potential for a more advanced therapy. Brahmwell reviews various chemotherapies and discusses the benefits of combining such therapies.

Therefore, given the above teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of any one of Cajot et al. (PTO-1449, C57), Katayose et al. (PTO-1449, C58) or Srivastava et al. (PTO-1449, C59) with Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) and treat tumor cells which are either positive or negative for functional p53 with viral expression constructs which express exogenous p53 such that the tumor cell is inhibited in growth with a reasonable expectation of success. Furthermore, one of ordinary skill in the art would have been motivated to combine the treatment as suggested by the combined teachings of Cajot et al. (PTO-1449, C57), Katayose et al. (PTO-1449, C58) or Srivastava et al. (PTO-1449, C59) with Liu et al. (Cancer Research, Vol. 54 (1994)) or Wills et al. (Human Gene Therapy, Vol. 5 (1994)) with that of Zhang et al. or Brahmwell and treat cancer with a combination of therapies known in the art to be effective to treat cancer. The ordinary artisan would have been motivated to combine these references because they all discuss therapeutic models for treating cancer.

Note, for the purposes of the 103 rejection, claims 140, 141, 144 and 145 have been interpreted to be directed delivery to the tumor site.

No claims are allowed.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on August 20, 1998, paper # 14 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(I). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen M. Hauda whose telephone number is (703) 305-6608.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian R. Stanton, may be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2801.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Papers related to this application may be submitted to Group 160 by facsimile transmission. Papers should be faxed to Group 160 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is or (703) 305-3014 or (703) 308-4242.

Karen M. Hauda
Patent Examiner
April 6, 1999

BRIAN R. STANTON, PH.D
PRIMARY EXAMINER